REMARKS

Claims 1-5 are pending for the examination. Upon entry of the accompanying amendment, claims 1-4 will be pending in the application and claim 5 will be canceled.

Claim 1 has been amended to incorporate the features of original claim 5. No new matter has been introduced.

Entry of the amendments and reconsideration of the application are respectfully requested.

Information Disclosure Statement

Applicants disclose and provide a copy of the B.C. Lalor reference (Lalor BC *et al.*, "Placebo-controlled trial of the effects of sugar gum and metformin on fasting blood glucose and serum lipids in obese, type 2 diabetic patients", University of Manchester Department of medicine, Diabetic Medicine, 1990, -4, Vol. 7, No. 3, pp. 242-245) in the Information Disclosure Statement which is being concurrently filed.

Claim Rejections-35 U.S.C. §103(a)

The Office has rejected claims 1 to 5 under 35 U.S.C. 103(a) as being unpatentable over Sanghvi *et al.*, U.S. Pat. Publication No. 2004/0109891 ("Sanghvi")[1] in view of Shell *et al.*, U.S. Pat. No. 6,340,475 ("Shell").

[1] The Sanghvi reference was erroneously identified as US Publication No. 2007/0109891, which should read "2004/0109891."

Sanghvi is replied upon to teach a composition for sustained release of metformin or a pharmaceutically acceptable salt, comprising metformin, at least one hydrophilic compound (preferably xanthan gum), at least one cross-linking agent (preferably guar gum, locust bean gum and mixtures thereof), and at least one diluent (additive). The Office also asserts that Sanghvi teaches the ratio of metformin to hydrophilic compound/cross-linking agent in the range of about 1:01 to about 1:2.

The Office acknowledges that Sanghvi fails to teach the combination of polyethylene oxide and xanthan gum.

Shell is relied upon to teach a composition comprising metformin hydrochloride and the advantages of using combinations of polyethylene oxide and xanthan gum to provide a greater controlled release of a drug.

Shell is also relied upon to teach a drug controlled release formulation comprising drugs in polymeric matrices that are water-swellable (preferably, polyethylene oxide having an average molecular weight of about 100,000 to about 10,000,000). The Office further asserts that Shell teaches xanthan gum as a preferable ingredient in the forumation. Shell is cited as a single reference to reject claims 1-5 as well. (Office Action, paragraph at pages 4-6.)

Applicants respectfully traverse the rejections for the following reasons.

The present invention, as described in the currently amended claims, is patentable over the combination of Sanghvi and Shell or Shell alone, because it has achieved the remarkable effect from the characteristic constitution which is neither taught nor suggested in Sanghvi or Shell.

In particular, the formulation according to an embodiment of the present invention comprises metformin or a pharmaceutically acceptable salt thereof as an active ingredient; a combination of a polyethylene oxide and a natural gum as a carrier for controlled release; and a pharmaceutically acceptable additive, **wherein the weight ratio of metformin or a pharmaceutically acceptable salt thereof : the carrier ranges from 1 : 0.01 to 1 : 1**.

Thus, the currently claimed formulation is defined to a specific combination of metformin and a carrier consisting of polyethylene oxide and a natural gum.

Meanwhile, Sanghvi teaches a composition comprising metformin, at least one hydrophilic compound (e.g., xanthan gum), at least one cross-linking agent (e.g., guar gum, locust gum and a mixture thereof) and at least one diluent (additive), **which does not comprise polyethylene oxide**.

Similarly, Shell teaches a composition comprising metformin hydrochloride, a water-swellable polymeric matrix (e.g., polyethylene oxide) and an additive, wherein the weight ratio of drug to polymer is 15:85 to 80:20, and teaches that polyethylene oxide may be combined with xanthan gum (see Col. 9). However, Shell fails to teach the specific ratio of the combination of polyethylene oxide and xanthan gum. In the Examples, Shell discloses only polyethylene oxide or xanthan gum alone, **not a combination thereof**.

Accordingly, Sanghvi and Shell fails to teach or suggest a formulation having the specific combination of the present invention, i.e., metformin and polyethylene oxide together with a natural gum.

The combination of (1) the use of the combination of polyethylene oxide and a natural gum, as a carrier, and (2) the specific ratio of the metformin or a salt and the carrier produces unexpected effects over Sanghvi or Shell.

The claimed composition of an embodiment of the present application **exhibits a markedly improved controlled metformin release characteristic over a long period without initial burst release** due to the specific combination of polyethylene oxide and a natural gum used as a carrier for controlled release and the relative amounts of metformin and the carrier (1 : 0.01 to 1 : 1).

Specifically, as can be seen from Figs. 1 to 6 of the present invention as well as from the following Tables A-C, the formulations prepared in Examples 1 to 12 of the present invention exhibit a continuous release pattern for 9 hours or longer. Table A summarizes the ratios and the time to release 90% of the drug ($t_{90\%}$) of the formulations provided in Examples 1 to 12. The t $t_{90\%}$ values are extracted from Figures of the present application.

Table A

Inventive formulation	Weight ratio of metformin : carrier (combination of polyethylene oxide and natural gum)	$t_{90\%}$*
Ex. 1	1 : 0.36	>10
Ex. 2	1 : 0.3	10
Ex. 3	1 : 0.3	10
Ex. 4	1 : 0.3	9
Ex. 5	1 : 0.4	>10
Ex. 6	1 : 0.4	10
Ex. 7	1 : 0.36	>10
Ex. 8	1 : 0.36	>10
Ex. 9	1 : 0.52	10
Ex. 10	1 : 0.52	10
Ex. 11	1 : 0.52	>10
Ex. 12	1 : 0.92	>10
* $t_{90\%}$: Time to 90% drug release		

In contrast, the formulation disclosed in Shell's patent which comprises metformin and a water-swellable polymeric matrix (a carrier for controlled release) in a weight ratio ranging from 15:85 to 80:20, **releases at least about 40% of metformin within one hour after immersion in gastric fluid and substantially all of metformin within about 8 hours**.

Especially, **the formulations prepared in Shell's Examples comprising polyethylene oxide or xanthan gum alone as the carrier** show $t_{90\%}$ values of 7.5 or lower, and the $t_{90\%}$ values of 7.5 is achieved only when the carrier is used in an amount larger than metformin as shown in Table B below.

Table II

Shell's formulation	Weight ratio of metformin : carrier		$T_{90\%}$*
Ex. 1 (Fig. 1)	metformin : polyethylene oxide	1:0.55	3.5
	metformin : polyethylene oxide	1:0.55	6
	metformin : polyethylene oxide	**1:2.13**	**7.5**
Ex. 4 (Fig. 4)	metformin : polyethylene oxide	1:0.25	4
	metformin : xanthan gum	1:0.25	3
Ex. 5 (Fig. 5)	metformin : polyethylene oxide	1:0.55	7
Ex. 7 (Fig. 7)	metformin : polyethylene oxide	**1:2.06**	**7.5**
	metformin : xanthan gum	**1:2.06**	**7.5**
* $t_{90\%}$: Time to 90% drug release			

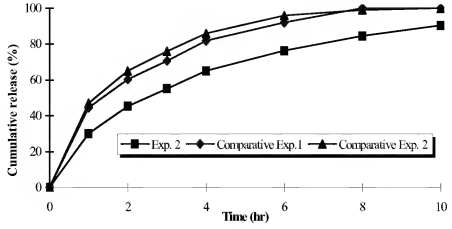
Thus, Shell's formulations show controlled release effects far inferior as compared with those of the currently claimed invention, even when a large amount of the carrier is used.

Furthermore, as can be seen from Fig. 4 of the present application and Table C below, the formulations of Comparative Examples 1 and 2 having polyethylene oxide or xanthan gum alone exhibit initial burst release of metformin and an unsatisfactory controlled release characteristic inferior to that of the inventive formulation (Ex. 2).

Table III

	Carrier for controlled release	Weight ratio of metformin : carrier	$t_{40\%}$	$t_{90\%}$
Ex. 2	Combination of polyethylene oxide and xanthan gum	1 : 0.3 (50 : 5+10)	1.7	9.4
Com. Ex. 1	Xanthan gum	1 : 0.2 (52.6 : 10.5)	0.9	5.6
Com. Ex. 2	Polyethylene oxide	1 : 0.1 (55.6 : 5.6)	0.9	4.8

Fig. 4



Based upon the results reproduced and discussed above, it is clearly that the currently claimed invention is patentable.

Therefore, reconsideration and withdrawal of the rejections are respectfully requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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